

Changing Times

Annual Oration: Royal Victoria Hospital, Belfast, October 2001

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The great majority of these Orations have been delivered by men, but since 1995 the medical staff have to some extent redressed the balance albeit belatedly, and Professor, now Dame Ingrid Allen gave the Oration in 1995. Last year Professor Jennifer Adgey gave the Millennium Oration. It gives me great pleasure to follow her as Orator and when I look down the list of previous Orators it makes me proud to join that distinguished company. At this moment it also makes me nervous.

Heraclitus was an ancient Greek; he was indeed a very ancient Greek. He lived in Ephesus around 500 BC but he was a man ahead of his time, and he is reputed to have said "there is nothing permanent but change". I have chosen the theme of "Changing Times" for this Oration and would like to discuss some aspects of changes which have taken place in recent times in this profession and in my own specialty.

The first of these is the effect of recent changes on Academic Medicine. I fear these have not been entirely beneficial. The late Gary Love, former Professor of Medicine in this Medical School, gave this Oration in 1988. It was entitled "Serving Two Masters". By that he meant serving two employers, the University and the National Health Service. As everyone knows it is difficult to serve two masters and recently these difficulties have been compounded. This is largely due to divergence which has arisen between the priorities and objectives of the University and those of the National Health Service. As Gary Love said, the cardinal aspects of academic medicine are patient care, teaching and research.

All medical staff, academic or otherwise are well acquainted with changes in patient care. The increasing complexity of modern medicine, the necessity for continuous up-dating and revalidation coupled with increasing expectation by the general public, is something which we are all learning to live with, not only in the medical

profession but in nursing and professions allied there-to. Similarly teaching is not the prerogative of academic medicine. A great deal of undergraduate medical teaching is carried out by NHS staff. This hospital has a long and proud tradition of teaching which I will return to later. Nonetheless with the introduction of the new medical curriculum by the GMC three years ago, there was a switch away from formal lectures to problem-based learning and small group teaching. The jury remains out on the efficacy of this type of teaching but it certainly takes a great deal more time and many more personnel to deliver. In my own specialty, demands for teaching time quadrupled.

The most controversial aspect of recent change in academic medicine has been with regard to research and the institution of the Research Assessment Exercise. This is a peer-review system commissioned by the Higher Education Funding Council which assesses universities on their research performance and determines to a considerable extent their funding for the next five years. Thus it has assumed very high priority in university life. Teaching and in particular patient care have been forced into the background. Indeed the great majority of university departments have no responsibility for patient care. Thus it rates a very low priority.

Assessment is based on three factors, the number and quality of peer-reviewed publications, number of research support staff and, most importantly income from research grants. The implication is that expensive research is good research. Consequently clinical academic staff find themselves under unrelenting pressure to pursue research grants and bring in income. Combining this with a heavy clinical commitment and

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teaching is a formidable task and one which for many is losing its appeal.

A meeting of Professors of Pathology throughout the UK was held recently to discuss this matter. It was probably a crisis meeting. The report of this meeting¹ written by an eminent pathologist and research worker pulls no punches. It states "it was felt strongly that the Research Assessment Exercise had been singularly unhelpful if not destructive, especially in the sphere of academic surgical pathology." I think the same applies to many specialties well beyond surgical pathology.

The result of these recent policies is not difficult to predict and is shown in Table I. These figures have been compiled by the Council of Heads of Medical Schools² and thus I think it is safe to assume they are authentic. It shows the considerable number of vacant posts at various levels in academic medicine throughout the United Kingdom in October 2000 and the number which have been vacant for more than six months. Bear in mind that ten years ago these posts were considered highly desirable. The most ambitious, the brightest and the best medical graduates would have been competing fiercely for these positions. Now it appears they are walking away. I think the General Medical Council and the Higher Education Funding Councils need to take a long and urgent look at the consequences of their policies in academic medicine. If the drift from academic medicine continues, who will take responsibility for undergraduate medical education?

TABLE I

Summary of Vacancies in Academic Posts in UK Medical Schools (as at 1/10/2000)

Data collected by Council of Heads of Medical Schools		
	<i>Posts unfilled</i>	<i>Posts unfilled for more than 6 months</i>
Professor	79	36
Reader/S Lecturer	145	81
Lecturer	177	98

I would now like to move on from that rather downbeat assessment to look at some of the changes that have taken place in my own specialty of tissue pathology in recent years. In a very different context Harold Macmillan coined the

phrase "the winds of change". Sometimes it feels almost like a whirlwind of change. The practice of tissue pathology or histopathology includes autopsy practice. Morbid anatomy is the depressing term often applied. Within the past few months this practice has come under intense scrutiny over the practice of tissue retention for teaching and research and retention of small tissue samples for microscopical examination. What was not only accepted practice but best practice, carried out for decades, indeed for centuries, has now in some cases become unacceptable in the absence of detailed consent. This is not a suitable forum in which to discuss this matter and I do not intend to do so. However few people outside the department are aware of the amount of time and energy that this controversy has consumed and I would like to acknowledge the enormous amount of effort put in by many members of the Pathology department as a result of this matter. Since January of this year the department has received over 1200 enquiries. These have been dealt with initially by the secretaries within the department and then by Dr. Maureen Walsh, Dr. Meenakshi Mirakhor in Neuropathology and in particular by Dr. Claire Thornton. Dr. Thornton and her secretary, Mrs. Claire Preshaw, have themselves dealt with over 1000 enquiries. These require detailed reference to records, in some cases going back 40 or 50 years. In all instances these enquiries have been dealt with in a patient, polite and understanding fashion and I think this Trust owes a debt to the people involved, particularly Dr. Thornton. The Trust has provided help in the form of a telephone helpline and a great deal of assistance in dealing with psychological aspects has been given by Dr. Nicola Rooney. No help has been provided by Government agencies or Coroners, despite the fact that many of these autopsies were carried out at Coroners' request. This has been a stressful matter on all sides.

One of the major changes in histopathology practice over the past 30 years has been the change in emphasis away from autopsy work to surgical pathology, the examination of tissue from the living patient with a view to establishing the diagnosis and the extent of disease. Table II compares the number of biopsy and operative specimens examined in pathology laboratories in Northern Ireland in 1970 and in the year 2000. There has been a marked increase in this activity over 30 years. This takes no account of screening

and diagnostic cytology which have increased almost exponentially. The number of autopsies carried out has remained roughly the same or fallen slightly in that period. Personally I welcome this change of emphasis greatly. On the technical side the great advance has been the advent of immunohistochemistry (ICC) whereby a labelled antibody is applied to a tissue section in order to identify cell and tissue types, gene products etc – the applications are multitudinous. This technique was refined and improved by Ludwig Sternberger in the 1970s. Shortly afterwards Professor Cesar Milstein working in Cambridge described the production of highly specific monoclonal antibodies.³ The application of these techniques has greatly increased and refined our diagnostic abilities.

Table II
*Surgical Pathology in N. Ireland
Specimens Reported*

	1970	2000
RVH	11150	23900
BCH	18050	18300
Altnagelvin	1850	11600
Antrim	–	13500
Craigavon	–	13000
Total	31050	80300

Now for a little bit of medical science. I would like to turn attention to some diseases in which I have had some interest over the years and in which there has been remarkable change in recent times. This change has been almost exclusively beneficial. The disease I would principally like to discuss is Peptic Ulcer Disease.

This term covers chronic gastric and duodenal ulcers. It is perhaps easy to forget how common this disease was even 30-40 years ago and how much misery, morbidity and not inconsiderable mortality it caused. It is still quite prevalent today especially in the elderly but the treatment and prognosis have changed completely. Surgery, which was a mainstay of treatment is now seldom necessary.

Reference to a prestigious textbook of Gastroenterology published in 1984 gives a variety of causes of chronic peptic ulcer disease.⁴ Many of the listed causes were perfectly valid. Aspirin and other non-steroidal anti-inflammatory

drugs are important causes of peptic ulceration particularly gastric ulcers and this has been increasingly recognised. Syndromes such as the Zollinger-Ellison syndrome and multiple endocrine neoplasia are also potent causes but account for only a very tiny proportion of cases; other causes listed are vague and not very relevant. Psychological stress was at that time considered very important. This may be so but it is not the basic underlying cause.

The first major step forward in treatment of this disease came from the pharmaceutical industry when James Black, who at that time was working with Smith, Kline and French, developed the first H₂ receptor antagonist drug Cimetidine or Tagamet. He was subsequently knighted and received a Nobel Prize for this work and deservedly so. This was the first really effective drug to suppress acid secretion in the stomach. The old adage “if there is no acid there is no ulcer” proved to be true, and in many cases treatment with cimetidine allowed these ulcers to heal. However it was noted that once treatment was stopped, a depressingly high percentage of ulcers recurred and really we were no further on in understanding why the ulcers occurred in the first place.

Then two letters appeared in the *Lancet* under a single heading,⁵ “Unidentified curved bacilli on gastric epithelium in active chronic gastritis.” The letters came from Perth in Western Australia. The first was written by Dr. Robin Warren a pathologist and the second by Dr. Barry Marshall who was at that time a trainee gastroenterologist. They described the presence of bacteria on the surface of the gastric mucosa, the lining of the stomach. Such bacteria had been described before but had been dismissed as mere contaminants. Marshall and Warren observed the crucial association between the presence of the bacteria and active chronic inflammation of the underlying gastric mucosa. In addition, with a lot of help from the then Professor of Microbiology in Perth, Stewart Goodwin, Marshall also managed to grow the bacteria in culture. A year later Marshall and Warren made the additional connection between the presence of bacteria and peptic ulcer disease in a paper published in the *Lancet*.⁶ Marshall is an articulate and flamboyant man who enjoys the limelight and is not one to hide his light under a bushel. Warren, on the other hand appears to be quiet and unassuming and seems happy to let others take the glory. You will I am sure,

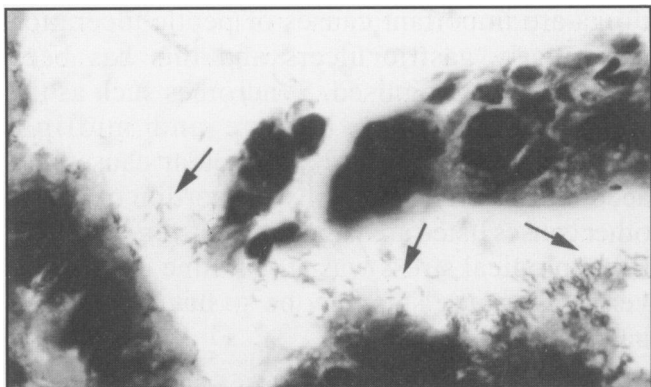


Fig 1. *Helicobacter pylori* organisms (arrows) on the surface of gastric mucosa in active chronic gastritis. Oil immersion. Giemsa.

immediately recognise these as the characteristics of a typical pathologist.

There was considerable reluctance to accept Marshall and Warren's hypothesis that peptic ulcer disease might in most cases may be an infectious disease. This was treated with scepticism and in some cases with derision. It was considered that colonies of bacteria could not survive for any length of time in the hostile environment of the human stomach with very low pH levels but they can and they do. Fig 1 shows the surface of the mucosa and the curved or spiral-shaped organisms which Marshall and Warren described. Viewed under the scanning electron microscope at a magnification of about 4000 they can be clearly seen on the surface of the gastric mucosa. Microbiologists rapidly developed methods of growing the organism in culture which is difficult. Unfortunately for the rest of us they kept changing its name and the bacterium became known by a series of names. Eventually it was decided that it belonged to a separate genus and the name of *Helicobacter pylori* was adopted. This is quite sensible as it refers to the spiral-shape of the organism and the fact that it is found mainly in the pyloric antrum.

Subsequent work carried out over the next few years showed that this is an exceedingly common infection. In Western countries by the time we reach middle-age, 50 or 60% of the population have this infection, in the developing world the incidence is almost 100%. What was perhaps more relevant was the finding that in 95% of patients with duodenal ulcer and in around 60% of patients with gastric ulcer the infection is present. However as I said, the hypothesis that infection and subsequent gastritis may lead to

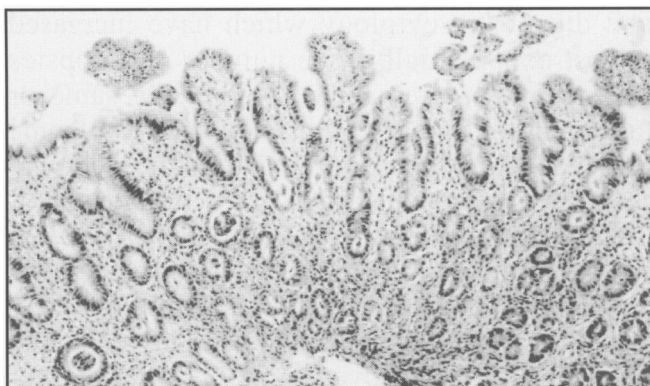


Fig 2a. Biopsy of gastric mucosa in *H pylori* gastritis. There is intense inflammation of the lamina propria with infiltration by polymorphs, plasma cells and lymphocytes. *H pylori* were present on the mucosal surface.



Fig 2b. Biopsy from the same patient 13 months after eradication of *H pylori* infection. The inflammatory infiltrate is much reduced. Polymorphs have disappeared and only small numbers of lymphocytes and plasma cells remain.

chronic ulceration was difficult to prove and was accepted only slowly. The most convincing evidence in favour of this hypothesis came from therapeutic trials. Histology helps illustrate this with regard to gastritis (Fig 2a and 2b).

Similar work provided convincing evidence of the beneficial effect of eradication of the infection on peptic ulcer healing. Such work was pioneered in Dublin by Professor Colm O'Morain's group.⁷ Similar findings are summarised in a later American study published in 1993.⁸ In patients treated with acid suppression therapy and antibiotic therapy to eradicate the organism, ulcers recurred in only 2% after treatment was stopped. In patients treated with acid suppression therapy alone and in whom the organism was not eradicated, ulcers recurred in 85% of cases. That is fairly convincing evidence and it was evidence

of this type that finally convinced even the sceptics that this infection is the principal cause of peptic ulcer disease.

Because *H. pylori* inhabits the mucus layer covering the gastric mucosa it is not easily attacked by the body's immune system and thus in most cases patients who contract the infection have it for the rest of their lives unless suitable treatment is administered. It has long been known that long-term inflammation pre-disposes to development of cancer and soon epidemiological studies carried out in various different countries indicated that there is an increased risk of gastric cancer in patients who have *H. pylori* infection. There is also an increased risk of malignant lymphoma of the stomach although this is much less common. Thus it became apparent that there are two principal outcomes to long-standing infection with *Helicobacter pylori*. In most cases (pathway 1), bacteria and subsequent gastritis are confined to the antrum. The chronic active inflammation eventually leads to atrophic gastritis and intestinal metaplasia in the antrum. This tends to be accompanied by increased levels of circulating serum gastrin, increased gastric acid and increased risk of peptic ulcer.

In the other pathway (pathway 2), the gastritis is more widespread and involves both the antrum and the acid-secreting corpus of the stomach i.e. a pangastritis. This gives rise to much more diffuse atrophic gastritis further diminishing the acid secretion and allowing the organisms to spread. Patchy change then takes place in the lining of the stomach whereby it comes to resemble the lining of the small intestine (intestinal metaplasia) and these patients are at slightly increased risk of developing gastric cancer.

In the past 10 or 15 years the morphological sequence of events, in other words the changes in the gastric mucosa which we can detect down the microscope have become fairly well defined. Everyone in whom the infection becomes established develops active gastritis. Most of these patients will develop some degree of atrophic gastritis and most will, over the years develop intestinal metaplasia. A small minority, especially among those in whom the disease process follows pathway 2, will go on to develop dysplasia which is a term for disordered growth and a significant proportion of those will develop carcinoma.

The question arises, can we interrupt this sequence of events before it reaches the dangerous stage. There is considerable debate about this but I believe that in the early stages this sequence can be stopped and perhaps reversed. Dr. Catherine Larkin carried out a study on the effect of eradication of *Helicobacter* on atrophic gastritis affecting the body of the stomach.⁹ She measured gastric acid levels and serum gastrin levels and found that in most cases these revert to normal after the organism is eliminated. These are markers of atrophic gastritis and their return to normal levels indicates reversal or at least lack of progression of this process. Histology supports this. Biopsies taken at the start of the study showed patchy mild or moderate atrophic gastritis of the mucosa of the corpus of the stomach in most patients with *H. Pylori* infection. Biopsies taken approx one year after eradication of the infection showed not only improvement of the active gastritis but in most cases partial regression of the atrophic gastritis. However none of the cases studied showed intestinal metaplasia on biopsy and it is likely that a point of no return is reached. Once intestinal metaplasia is established, it is doubtful if the mucosa will revert to normal.

The incidence of gastric cancer has been falling throughout the world quite dramatically which can only be good news. However there is a sting in the tail – there is always a sting in the tail. The sting is associated with Barrett's oesophagus. In this condition the normal lining of the lower oesophagus is replaced by patches or tongues of gastric mucosa which have moved upwards in a cephalic direction. It is thought to be due to reflux of acid contents in the stomach upwards into the oesophagus. In these circumstances the normal lining of the lower oesophagus changes to resemble that of the stomach. Barrett's oesophagus is usually fairly harmless. It causes heartburn and sometimes ulceration but in a small number of cases it progresses to adenocarcinoma of the lower oesophagus or the junction between the oesophagus and stomach as shown here. This tumour is highly aggressive and while incidence of cancer of the more distal stomach has declined considerably the sting in the tail is that adenocarcinoma of the lower oesophagus and upper end of the stomach has increased recently. This was first noted in the early 1980s and reported in 1991 and the trend has continued.

I had the pleasure of working with Dr. Catherine Gleeson when she did her PhD under the

supervision of Dr. Hilary Russell. In her PhD Kate studied the molecular biology of Barrett's oesophagus and related adenocarcinoma. She published a series of good quality papers and among other things identified chromosomal loci which may be involved in progression of Barrett's epithelium to cancer.¹¹ In addition her molecular studies supported the theory that there is a step-wise sequence leading from relatively normal mucosa to malignancy similar to that already described in the stomach.¹² This progression consists of replacement of the squamous epithelium of the lower oesophagus by columnar epithelium i.e. Barrett's oesophagus. The next step is development of intestinal metaplasia in Barrett's mucosa. In a tiny proportion of such cases Dr. Gleeson detected molecular changes at this stage similar to those in fully fledged cancer despite the fact that there was nothing alarming in the histology. In a small proportion of cases intestinal metaplasia proceeds to dysplasia and in a further minority to invasive adenocarcinoma.

I should state, in case I sound alarmist, that the risk of developing adenocarcinoma in Barrett's oesophagus is quite low. Earlier studies indicated that the risk was increased by approximately 40-150 times but Dr. Liam Murray has compiled a sizeable series of local cases which have been followed up for a considerable number of years. His findings indicate that the risk of cancer associated with Barrett's oesophagus is approximately fifteen times that of the rest of the population and considerably less than earlier estimates.¹³

The challenge in the future will be to identify the relatively small number of patients who are at risk of developing cancer well before they actually do so. At present histological detection of dysplasia remains the basis for this but histology in its present form is a fairly blunt instrument. Hopefully improved molecular biology techniques such as those used by Dr. Gleeson or perhaps computer assisted image analysis of biopsy material will identify potentially dangerous abnormalities within cells with greater precision than we have at present and will thus be able to identify patients at risk at an earlier stage long before cancer develops. That remains the goal with this particular cancer and indeed with most cancers.

Finally I would like to turn to the changes taking place on this site. They are quite momentous and

are there for all to see. We are moving from the familiar but rather tired facade fronting onto the Grosvenor Road to a new building. More importantly we are moving from wards which have barely changed since the Edwardian era. Phase I of the new building is now complete and we have a pristine brand new hospital which will hopefully provide much needed improvement in facilities for patients, relatives and staff alike. I do hope that we can keep it in that pristine state of cleanliness. Unfortunately on this site, parts of the estate are in a very run-down condition. There is an abundance of litter, a dearth of litter bins and in some places fixtures and fittings are in a dilapidated state. Litter and vandalism are sadly endemic in this country and 20 years of under-funding on this site mean that there is little money left over for site maintenance after provision of clinical services. Hopefully with the opening of the new hospital things will change for the better.

It is of course very easy to blame management for everything. We all have our pet gripes. In Laboratory Medicine for instance, Haematology has been moved off this site and we find it difficult to understand how a hospital such as this, containing a major trauma centre, obstetrics and substantial cancer services can function optimally without the presence of Consultant Haematologists on site. It is however worth remembering that in the early 1990s there was a real danger that the Royal Victoria Hospital would be downgraded and that acute hospital services would be moved off this site. Instead it remains a centre point of hospital services and referrals for the Province and we have the first phase of the new hospital. To achieve this U-turn has required determination, intensive lobbying and involvement in politics at the highest level by our management team. Few of us are aware of the amount of effort involved particularly on the part of the past and present Chairmen of the Trust and our Chief Executive Mr. William McKee. The cost of phase I of the new hospital has been 47 million pounds. The completion was supposed to take place in 36 months. In fact it took 30 months. The builders also deserve great credit for completing ahead of schedule and for causing much less disruption to the everyday running of the hospital than many of us anticipated. Phase II will cost 67 million pounds.

The purpose of the Oration is not to give the Orator a chance to indulge himself. The purpose is to welcome new students to this hospital and I

bid you a very warm welcome. I have spoken briefly about the long and proud tradition of teaching in this hospital and I have no doubt it contributes to the high reputation of Queen's Medical School as a teaching centre. All aspects of professional life are now subject to scrutiny and assessment. Teaching is no exception. In the last Teaching Quality Assessment this Medical School was rated highly. In soccer parlance it is well in the top half of the Premiership division. The Dental School did even better, indeed it could not have done any better. It won the equivalent of the league and cup double. Such standards will be hard to maintain but as this hospital is in the forefront of teaching I am confident we can offer you a good medical and dental education. I wish you well in your careers. It will be demanding but hopefully rewarding. The care and welfare of your patients will be your first priority. I wish you well with your patients and also with the colleagues you will be working with.

There are a number of people I have to acknowledge with regard to this Oration. First, foremost and most importantly are the colleagues I have worked with for many years in the Pathology Department on this site. Very few people are as lucky as I have been in this respect with regard to colleagues at all grades and levels. To these colleagues I am exceedingly grateful. Most of them have a healthy sense of humour and I would recommend this as an essential ingredient for harmonious relations.

I would like to acknowledge the late Mr. Terence Kennedy and the late Mr. John Gibbons. They were both expert surgeons. Terence Kennedy specialised in surgery of the stomach and treated many cases of peptic ulcer and gastric cancer. In addition he was a skilled endocrine surgeon and together with Keith Buchanan and Teddy McIlrath raised treatment of neuroendocrine tumours in this Province to world-class levels. John Gibbons was a highly skilled thoracic surgeon and a marvellously friendly and sociable person. These men had very different personalities but had much in common. They were excellent surgeons with a busy workload. Not only did they have to treat everyday disease but for many years like all their surgical colleagues they had to treat horrendous trauma caused by terrorist activity. Lesser men might have wilted but they did the very opposite. They possessed sharp and enquiring minds and had the ability to see beyond the

everyday routine. They were constantly sparking off ideas and research projects for younger colleagues. Many of us benefited greatly from knowing them.

There are several colleagues outside pathology, too numerous to mention individually in this article whom I gratefully acknowledge. They include gastroenterologists, endocrinologists, surgeons, radiologists, epidemiologists, molecular biologists and computer experts. A few have retired, others are at the peak of their careers and some are starting out. It has been a pleasure and an education to work with them. They have all contributed greatly to the work of this hospital and if we can continue to recruit and retain people of this calibre – and we will have to work at it – then the future of this hospital is assured.

While on the subject of change one final piece of mild black humour – “If you are in a bad situation, don't worry, it'll change. If you are in a good situation, don't worry, it'll change”.¹⁴

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Date: 4 October 2001.

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